Cancel Claims 10, 11 and 12.

Add the following new Claims:

13. A composition of Claim 9 wherein the amount of the R(-) isomer of albuterol is greater than approximately 90% by weight of total albuterol.

B3

14. A composition of Claim 13 wherein the amount of the R(-) isomer of albuterol is greater than approximately 99% by weight of total albuterol.

REMARKS

Rejection of Claims 1-12 under 35 U.S.C. §103

Claims 1-12 have been rejected under 35 U.S.C. §103 over Chemical Abstracts which, it was stated, teaches salbutamol (albuterol) used to treat asthma and compositions containing albuterol. It was further stated that the determination of a particular isomer would be a matter of obvious alternatives. Finally, it was stated that difference in activity between isomers is not unexpected (In re Adamson et al.).

Applicants respectfully traverse this rejection. The Chemical Abstracts reference shows the bronchodilator effects of salbutamol and drug combinations incorporating salbutamol. This reference does not teach nor suggest the use of an optically pure isomer of salbutamol, either alone or in combination with other drugs. From this reference, a person of ordinary skill in the art would not be

motivated to use an optically pure isomer of salbutamol to result in bronchodilation because there is no suggestion of the efficacy of such an isomer in the reference.

In re Adamson et al. does not cure this defect in the Chemical Abstracts reference. In re Adamson et al. teaches that optical isomers, or methods of separating such isomers, of compounds that are art recognized as having optical isomers are unpatentable. In re Adamson et al. indicates that physiological behavior of the stereo-isomers can differ considerably. However, In re Adamson et al. is not directed to the patentability of methods of eliciting physiological responses, such as treating asthma, of optically pure isomers. More importantly, neither the Chemical Abstracts reference nor In re Adamson et al. teaches or suggests the use of R(-) albuterol to result in bronchodilation. Applicants' disclosure teaches this method. The Chemical Abstracts reference does not indicate or suggest the use of the R(-) isomer of salbutamol and In re Adamson et al. does not teach the efficacy of this isomer but, rather, at best, that this isomer will have a different physiological behavior than the S(+) isomer. For example, from In re Adamson et al., it could be inferred that the physiological property of the R(-) isomer is a toxic effect. Applicants' disclosure, instead, teaches the bronchodilation efficacy of this isomer.

Rejection of Claims 1-5 under 35 U.S.C. §103

Claims 1-5 have been rejected under 35 U.S.C. §103 as being unpatentable over Brittain et al., Hartley et al., Hawkins et al. and Buckner et al, who, it was stated, teach compositions containing the claimed compounds and its isomers used as a bronchodilator in the treatment of asthma. It was further stated that the references teach greater bronchodilation activity of the R(-) isomer over the S(+) isomer, so compositions containing namely the R(-) isomer in the treatment of asthma is clearly rendered obvious by the prior art.

Applicants respectfully traverse this rejection. Brittain et al. show that both isomers and the racemic mixture of salbutamol act on $beta_2$ receptors rather than the $beta_1$ receptors. The (-) isomer and the racemic mixture are roughly equipotent against bronchospasm in guinea pigs (see page 145, last full paragraph) and isolated guinea pig trachea (see page 146, Table 1 and last full paragraph). That is, Brittain et al. show that there is no significant difference in bronchoactivity between (-) salbutamol and the racemic mixture of salbutamol.

Similarly, Hartley et al. show that both isomers and the racemic mixture of salbutamol act on the $beta_2$ receptors rather than the $beta_1$ receptors. The effects of the (-) isomer and the racemic mixture are equiactive on the $beta_2$ receptors of the intact trachea of the guinea pig (see the next to last paragraph of the second column on page 895). Indeed, Table I indicates the racemate of salbutamol is

somewhat more active than the (-) isomer; the mean equipotent doses of racemic and (-) albuterol were reported in Table I to be 4.3 and 6.6, respectively..

Hawkins et al. characterize this study of Hartley et al. by stating that Hartley et al. "reported that racemic salbutamol was 1.5 times as active as the more active (levo) of the two enantiomers." Hawkins et al., in their study, show that the (-) isomer of salbutamol is more active than the racemic mixture when applied against guinea pig tracheal chains (see page 857, top of left column) -- a result that is clearly at odds with the findings of Hartley et al.

Buchner et al. show that the (-) and (+) isomers of salbutamol are more active on guinea pig tracheal strips than on guinea pig atria. There may be more potency for the (-) isomer than the (+) isomer on the tracheal strips, but there is no indication of the potency of the (-) isomer of salbutamol compared with the racemic mixture. This reference is silent concerning the relative efficacy of the (-) isomer and the racemic mixture.

The study by Buckner et al. attempts to ascertain whether the ratio of activity of albuterol (salbutamol) and other beta-agonists towards isolated trachial strips and isolated right atria (in both cases from guinea pig) is dependent on the stereochemistry of the tested drug. These investigators summarize their results as follows (see the right-hand column on page 619): "Even though the potencies of single isomers may differ as much as 24-fold (for salbutamol) between atria and trachea, the stereoselectivity for production of activity is

the same." That is, the ratio of tracheal-to-atrial activities found by Buckner and Abel for the (-) and (+) isomers of albuterol were identical.

These references can be interpreted as indicating that the (-) isomer of salbutamol may not be as effective as the racemate. Since there is lack of agreement between these references concerning the relative efficacy of the (-) isomer and the racemate, a person of ordinary skill in the art would be, at least, confused by these references. For example, if Brittain et al. or Hartley et al were considered, there would be no apparent difference in efficacy between the (-) isomer and the racemate.

In contrast, Applicants' invention teaches the use of R(-) albuterol rather than the racemate to result in bronchodilation. By such administration of the R(-) isomer, the undesirable side effects associated with the racemate are also reduced. Applicants' invention clearly distinguishes over the prior art by specifying the R(-) isomer, rather than the racemate or the S(+) isomer, to result in bronchodilation and to reduce undesirable side effects associated with beta-adrenergic drugs.

Rejection of Claims 6-12 under 35 U.S.C. §103.

Claims 6-12 have been rejected under 35 U.S.C. §103 as being unpatentable over the references cited in the rejection of Claims 1-5 in further view of the Chemical Abstracts reference which shows combinations of drugs, including salbumatol, used in the treatment of asthma.

Applicants respectfully traverse this rejection. The Chemical Abstracts reference does not cure the above discussed shortcomings of the prior art in indicating the

use of R(-) albuterol to result in bronchodilation. The Chemical Abstracts reference does not show the existence or indicate a use for R(-) albuterol. There is no teaching or suggestion in the Chemical Abstracts reference that would motivate a person of ordinary skill in the art to use R(-) albuterol alone or in combination with other drugs in the treatment of asthma. The cited references do not show nor suggest a combination of drugs that include R(-) albuterol to result in bronchodilation.

Rejection of Claims 6 and 9-11 under 35 U.S.C. §112, second paragraph.

Claims 6 and 9-11 have been rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. It was stated that there is no basis in Claim 9 for the mixture of isomers set forth in Claims 10 and 11. That is, Claim 9 is incorrect in not including the R(-) isomer. It was also stated that Claims 9-12 are too broad absent proportions of ingredients. It was stated that the term "additional drug" in Claims 6 and 9-11 is too broad.

In response to this rejection, Claims 2, 3, 6, 8 and 9 have been amended, Claims 7 and 10-12 have been cancelled and Claims 13 and 14 have been newly added. The amendments to Claims 6 and 9 state the constituency of the "additional drug". Since this constituency had been stated in Claims 7 and 12, these latter claims have been cancelled. Claim 8 was amended to state the proper dependency. Claim 9 was also amended to state the R(-) isomer of albuterol so that Claims 10 and 11 (now Claims

13 and 14) now have proper basis. Claims 2 and 3 were amended by adding the phrase "of total albuterol" to more distinctly claim the subject matter of the invention. Support for this amendment can be found on page 3, lines 25-30 of the specification. Finally, Claims 10 and 11 have been cancelled and replaced by Claims 13 and 14, respectively. These newly added claims are restatements of cancelled Claims 10 and 11 in better grammatical format and are in accordance with Claims 2 and 3.

Applicants respectfully traverse the rejection of Claims 9-12 (now Claims 9, and 13-14) as too broad absent proportions of ingredients. Such proportions are dependent on a number of factors known to a person of skill in the art. These factors include, for example, the individual's age, body proportions, type of disease, severity of symptoms and mode of administration (see the present specification page 4, line 22-page 5, line 2). For this reason, the proportions of ingredients cannot be stated with certitude for all individuals but, rather, must be determined on an individual basis. Skilled artisans determine the ingredient proportions based, at least in part, on the above-listed factors.

CONCLUSIONS

With the above amendments and for the above stated reasons, Applicants believe the 35 U.S.C. §§103 and 112, second paragraph rejections have been overcome. Applicants respectfully request reconsideration of the Application and allowance thereof.

If the Examiner feels that a telephone conversation would expedite prosecution of this Application, he is asked to call Applicants' Agent at (617) 861-6240.

Respectfully submitted,

Richard W. Wagner

Richard W. Wagner
Agent for Applicants
Registration No. 34,480

Lexington, MA 02173

Dated: September 23, 1991